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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,880	12/07/2005	Alan Cuthbertson	PN0384	2898

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IP DEPARTMENT
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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
08/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,880	CUTHBERTSON ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-11* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Inventorship

In view of the papers filed 8/16/2007, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding Anthony Eamon Storey, Harry John Wadsworth, Nigel Anthony Powell and Philip Duncanson.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 – 7 and 9 – 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 4 of U.S. Patent No. 6,264,914. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to compositions of formula V-L-R wherein V is an organic group having binding affinity for an angiotensin II receptor, L is a linker moiety, and R is a reporter moiety. The reporter moiety includes radionuclides conjugated to a chelating ligand; the linkers include amino acids; and the compounds are used for methods of imaging a human or animal subject.

Claims 1 – 7 and 9 – 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 10 of U.S. Patent No. 6,921,525. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to compositions of formula V-L-R wherein V is an organic group having binding affinity for an angiotensin II receptor, L is a linker moiety, and R is a reporter moiety. The reporter moiety includes radionuclides conjugated to a chelating ligand; the linkers include amino acids; and the compounds are used for methods of imaging a human or animal subject.

Claims 1 – 7 and 9 – 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 5 of U.S. Patent No. 7,182,934. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to compositions of formula V-L-R wherein V is an

organic group having binding affinity for an angiotensin II receptor, L is a linker moiety, and R is a reporter moiety. The reporter moiety includes radionuclides conjugated to a chelating ligand; the linkers include amino acids; and the compounds are used for methods of imaging a human or animal subject.

Claims 1 – 7 and 9 – 11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 10 of copending Application No. 10/541,949. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to compositions of formula V-L-R, or V-L-Z, wherein V is a vector having binding affinity for an angiotensin II receptor, L is a linker moiety, and R is a reporter moiety, as in the instant case, or Z is a chelating agent carrying an imaging moiety, as in the '949 application. Both sets of claims teach the same chelators, the imaging moiety may be a radionuclide, and the compounds are used for methods of generating images of a human or animal body.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 3 –7 and 9 – 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a compound of formula 1, wherein

V is an organic group having affinity for the angiotensin II receptor. However, the metes and bounds of the claims are unclear as to what types of structures are to be encompassed by such a functional description. For example, the specification defines a few specific examples of imidazole Ang II antagonist ligands including losartan, valsartan, candesartn and eprosartan (paragraph 0023), but it is unclear from such a limited disclosure of a few specific examples what other structures out of any and all possible organic groups would be capable of having angiotensin II receptor binding affinity. As such, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained.

Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6 and 7 recite the limitation "the chelating agent" in lines 1 – 2 of the claims. There is insufficient antecedent basis for this limitation in the claim because the claims are dependent upon claim 1, but there is no requirement for a chelating agent in claim 1.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to a contrast agent according to claim 1 where L additionally comprises... "PEG-like components," in line 3 of the claim. It is unclear what types of components are to be encompassed by the term "PEG-like."

Claims 9 –11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a pharmaceutical formulation, method of generating

enhanced images, or a kit comprising an effective amount of a compound of general formula 1. However, there is no description of what formula 1 is to represent in the claims, and are unclear what formula 1 is to include. While formula 1 is claimed in claim 1, claims 9 – 11 are not dependent upon claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 – 3, 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaveness *et al.* (US 6,264,914).

Klaveness discloses compositions of the formula V-L-R, where V is an organic group having binding affinity for an angiotensin II receptor site, L is a linker moiety, and R is a moiety detectable in *in vivo* imaging of a human or animal body (abstract). The composition may be used to image cardiovascular diseases and disorders. Losartan is a preferred vector (column 2, line 67; column 3, line 17). Most commonly, the linker comprises two or more reactive moieties connected by a spacer element (column 13, lines 18 – 20). The spacer may be include polyamino acids, homo- and co-polymers of lysine, glutamic acid and aspartic acid, and polypeptides (column 14, lines 21 – 23). See also column 19, lines 39 – 45. The reporter groups include metal radionuclides, such as 90Y, 99mTc, etc. chelated by chelant groups on the linker moiety (column 23, line 55 – column 25). An exemplified compound is a Tc chelate of N-(N-MAG-3-glycyl)-Losartan (claim 2, compound v).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 –3, 6, 7 and 9 – 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (US 6,264,914) in view of Archer *et al.* (WO 03/006070).

Klaveness discloses compositions of the formula V-L-R, where V is an organic group having binding affinity for an angiotensin II receptor site, L is a linker moiety, and R is a moiety detectable in *in vivo* imaging of a human or animal body (abstract), as set forth above. A variety of chelating moieties may be used to chelate a radionuclide as the reporter moiety, R (see column 24 – 25). An exemplified compound is a Tc chelate of N-(N-MAG-3-glycyl)-Losartan (claim 2, compound v).

Klaveness teaches that a variety of chelating agents are suitable for binding the radionuclude, but does not specifically teach those of formula II, as claimed in instant claims 6 and 7.

Archer teaches improved chelator conjugates with biological targeting molecules, suitable for forming metal complexes with radiometals, which are useful as radiopharmaceuticals, especially with ^{99m}Tc (abstract). Such chelators include those such as in Formula II, wherein Y is $-(A)_n$-X-Z. A_n is a linker moiety, such as CR_2, where R is H, C_{1-10} alkyl, etc.; X is NR^4, etc.; and Z is a biological targeting moiety, including synthetic receptor-binding compounds, etc. (page 4). The radiometal complexes may be prepared by reacting a solution of the radiometal in the appropriate oxidation state with the chelate conjugate at the appropriate pH, and may include the addition of a reducing agent (page 14, lines 1 – 15).

Archer does not specifically teach that the biological targeting moiety has binding affinity for an angiotensin II receptor.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the diaminedioxime chelators taught by Archer as the chelating agent employed in the V-L-R compounds taught by Klaveness. Klaveness teaches that a variety of chelating agents may be employed to bind a radionuclide. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so, because the diaminedioxime chelators are taught in the prior art to be functional equivalents for use in binding radionuclides, as shown by Archer.

Claims 1 – 5, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (US 6,264,914) in view of Pastan *et al.* (US 2004/0018203) and Arbogast *et al.* (US 7,211,240).

Klaveness discloses compositions of the formula V-L-R, where V is an organic group having binding affinity for an angiotensin II receptor site, L is a linker moiety, and R is a moiety detectable in *in vivo* imaging of a human or animal body (abstract), as set forth above. The linker moiety may be a peptide, etc. (column 14, lines 21 – 23). See also column 19, lines 39 – 45. An exemplified compound is a Tc chelate of N-(N-MAG-3-glycyl)-Losartan (claim 2, compound v).

Klaveness teaches that a variety of linker moieties may be used, but does not specifically teaches pegylated amino acids or branched amino acids.

Pastan discloses compositions comprising a targeting moiety linked to an effector molecule through a connector molecule, which connector molecule comprises one or more polyethylene glycol molecules. The targeting molecule may be a ligand, etc. (paragraph 0013). The connector molecule is a peptide (paragraph 0018). The effector molecule may be a radionuclide, a detectable label, etc. (paragraph 0020). Conjugation of PEG to a peptide linker provides increased circulation time, etc. (paragraph 0033 – 0034).

Arbogast discloses multivalent constructs which bind to a targeting agent (column 5, lines 20+). Such constructs include a diagnostic or therapeutic moiety chelated to a chelating moiety, such as a radionuclide (column 6, lines 5+). The

chelators may be linked to a targeting moiety via a variety of linkers, including linear, branched, or cyclic amino acids (column 42, lines 54 – 56).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to provide pegylated amino acids or peptides as the linker in the composition of Klaveness. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Pastan discloses that conjugation of PEG to a peptide linker provides increased circulation time, etc. such as in linkers to which PEG is conjugated to a peptide linker and metal chelates (paragraph 0033 – 0034). It would have been further obvious to utilize branched amino acids as the linker because Klaveness teaches that a variety of linking moieties can be used, including various amino acid and peptide linkers, and because Arbogast shows that linear, branched, etc. amino acids are well-known in the art for linking chelating moieties to a chelating agent.

Claims 1 – 3 and 9 – 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (US 6,264,914) in view of Yang *et al.* (US 6,692,724).

Klaveness discloses compositions of the formula V-L-R, where V is an organic group having binding affinity for an angiotensin II receptor site, L is a linker moiety, and R is a moiety detectable in *in vivo* imaging of a human or animal body (abstract), as set forth above.

Klaveness does not specifically teach a kit for the preparation of a radiopharmaceutical composition comprising a ligand-chelate conjugate and a reducing agent.

Yang discloses ^{99m}Tc chelates which are conjugated to a variety of ligands for tissue-specific imaging. Kits for the use in tissue-specific disease imaging are also provided (abstract). Kits are provided for preparing a radiopharmaceutical preparation. The kit generally includes a sealed via or bag, or any other kind of appropriate container, containing a predetermined quantity of an ethylenedicysteine-tissue specific ligand conjugate composition and a sufficient amount of reducing agent to label the conjugate with ^{99m}Tc. In certain cases, the ethylenedicysteine-tissue specific ligand conjugate composition will also include a linker between the ethylenedicysteine and the tissue specific ligand. The tissue specific ligand may be any ligand that specifically binds to any specific tissue type (column 4, lines 25 – 40).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to provide the compositions of Klaveness in the form of a kit comprising a reducing agent because both Klaveness and Yang teach targeted ^{99m}Tc chelates, and because Yang teaches that such reducing agents are useful in kits for providing radiopharmaceutical preparations (column 4, lines 25 – 40). One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Yang teaches a reducing agent, such as stannous chloride to be important for the reduction of Tc to its 4+ oxidation state (column 8, lines 49 – 64).

Claim Objections

Claim 4 is objected to because of the following informalities: in line 4 of the claim, the term "diclycolyl" appears, which appears to be a typographical error which is intended to read "diglycolyl". Appropriate correction is required.

Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER